REMARKS

Claims 13-29, 34, 36 and 42-68 are pending in the case, new claims 57-68 having been added by the present amendment. Support for the new claims can be found in the specification, e.g., in Examples 5 and 6 on pages 8-9. Claim 51 has been amended to clarify its scope. No new matter has been added. All claims remain under examination.

Rejection for obviousness-type double patenting

Claims 13-15, 17, 19, 20, 22-25, 34, 36, 42 and 53 remain provisionally rejected for obviousness-type double patenting over claims 13-15, 17, 19, 20, 22-25, 30-36, 38 and 42 of copending application no. 09/367,950. The claims of application no. 09/367,950 have not been allowed. Applicant reiterates (and thanks the Examiner for acknowledging) applicant's stated intent to file a terminal disclaimer in one of the two applications if such is still deemed appropriate once the claims of the two applications are allowed.

Rejections under 35 USC § 103(a)

As in previous Office actions, the present Office action dated March 4, 2010, asserts that claims 13-15, 17, 18, 20-29, 34, 36 and 42-56 are obvious over Carling, and that the remaining claims (claims 16 and 19) are obvious over a combination of Carling, Aberg et al. and Ryrfeldt et al. Applicant again traverses.

The rationale for the rejection is set out on pages 6-9 of the present Office action. As it is essentially identical to the rationale stated in prior Office actions (e.g., those dated September 19, 2008, and June 12, 2009), Applicant begins by reaffirming the arguments provided at pages 8-20 of Applicant's Reply filed March 18, 2009, and subsequently incorporated by reference at page 2 of the Reply filed December 11, 2009. Rather than repeat those arguments here, Applicant again simply incorporates them by reference into the present Reply and focuses instead on just a few of the points made on pages 13-17 of the present Office action, plus some additional evidence of nonobviousness newly presented below.

According to the present Office action at page 13,

> The skilled artisan would have been motivated to instruct the patient to use the Carling et al. composition as needed on the bases of up to 8 inhalations a day is for reasonable expectation of successfully achieving maximum benefit in the treatment of any level of the asthma condition, including an increase in asthma symptoms, acute asthmatic condition, maintenance treatment, and common asthma triggers. Additionally, due to the urgency of therapy during an asthma attack, a patient would obviously seek relief with the medication without consulting with the physician, in knowing the safe daily dosage range of each medication. (Informal English in the original)

The Examiner cites no evidence to support these assertions. As Applicant has previously pointed out, Carling et al. explicitly teaches (at page 6, lines 22-23) that "[t]he intended dose regimen" for the budesonide/formoterol combination "is a twice daily administration." Carling et al. goes on to say in the same sentence that this twice-daily administration suitably delivers a daily dose of formoterol "in the range of 6 to 100 μg." Even if a physician prescribed for a given patient a daily dose of budesonide/formoterol containing the maximum 100 μg daily dose of formoterol, and told the patient to inhale this as eight inhalations containing 12 μg formoterol each (as delivered by some of the inhalers exemplified at pages 7-9), this would mean four inhalations in the morning and four more in the evening in order to achieve the "twice daily administration" taught by Carling et al. It would be improper to read into Carling et al. a suggestion that the patient could spread up to eight inhalations throughout the day on an as-needed basis, where this reference so clearly says that the "the intended dose regimen is a twice daily administration." Further, there is no basis in Carling et al., or anywhere else in the art, for the Examiner's assertion that a patient would "obviously seek relief" with the budesonide/formoterol combination during an asthma attack. Though Carling et al. does use the term "rescue medicine" at page 4, line 8, the context of this phrase shows that Carling et al. was simply describing the rapid onset of action of formoterol (a long-acting β2 agonist) when used in a twice-per-day maintenance regimen, compared to the slower onset of other long-acting β-agonists such as salmeterol. There is no suggestion in Carling et al. that the budesonide/ formoterol combination should be taken more than twice per day, and certainly no suggestion that it be taken "as needed" or for relief during an acute asthma attack. In fact, the sentence at the end of the paragraph that

mentions "rescue medicine" clearly states how the budesonide/formoterol combination should be used: "**The combination according to the present invention permits a twice daily dosing regime as a basic treatment of asthma, including nocturnal asthma**." (emphasis added) One of ordinary skill in the art would understand Carling et al. to have intended that the combination be administered in precisely the daily amount prescribed by the physician, no more and no less, and that the daily amount should be divided into two administrations each day—presumably one in the morning and one in the evening. For emergency relief of an asthma attack, one of ordinary skill in the art knew to use short-acting β2 agonist bronchodilators such as terbutaline, and not long-acting β agonists such as formoterol or medications containing budesonide or other glucocorticosteroids. Patients were (and still are) prescribed inhalers containing such short-acting β2 agonists for emergency use, separate and distinct from the inhalers they may be prescribed for twice-daily maintenance therapy.

In contrast to the utter lack of evidence provided by the Examiner to support her assertions, Applicant has submitted extensive evidence that one of ordinary skill would NOT have instructed the patient to inhale the Carling et al. composition "as needed" or during an acute asthma attack or in any context other than the prescribed twice-per-day fixed dose, and that a patient would NOT have inhaled further doses of the composition (beyond the prescribed twice-per-day maintenance doses) without consulting with the physician, whether during an asthma attack or not. One such item of evidence submitted by Applicant is the prior art Pulmicort Turbuhaler® budesonide product insert that is Exhibit 1 filed with Applicant's Reply dated July 27, 2007. Applicant submitted this product insert to illustrate that those of ordinary skill in the art at the priority date knew that budesonide should be administered no more than twice per day, and certainly not "as needed". (See the discussion of this Exhibit 1 in Applicant's July 27, 2007 Reply, and note, for example, the sections of Exhibit 1 hand-labeled "G","C", and "F", respectively: **"Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of PULMICORT TURBUHALER in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.... The patient**

should not alter the prescribed dosage unless advised to do so by the physician…. If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed to contact the physician…. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur (see PRECAUTIONS).") These instructions stem from the fact that budesonide is a corticosteroid, and like other drugs of that class can induce dangerous side effects in patients. Thus, the physician is cautioned to prescribe the "lowest effective dose" for administration on a regular basis, twice per day, and to warn the patient not to take a larger dose than prescribed. See also the text of Exhibit 1 immediately above the section labeled "I" on page 2: **"This medicine is NOT intended to provide rapid relief of your breathing difficulties during an asthma attack. It must be taken at regular intervals as recommended by your doctor, and not as an emergency measure."**

Rather than acknowledge that the budesonide product insert of Exhibit 1 would have *taught away* from the presently claimed methods, or explain why she believes it would not have done so, the Examiner simply dismisses the evidence out of hand. The Examiner's rationale for dismissing the evidence appears to be based on the misconception that Applicant is citing the budesonide product insert evidence as evidence of "unexpected results." (See the present Office action at page 15, lines 2-4, which says "It is noted that evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention." Further, the Office action relies for support on two cases, *In re Kulling* and *In re Grasselli*, each of which involved evidence of unexpected results but did not even mention teaching-away evidence.) To be clear: Applicant is citing the budesonide product insert as a *teaching-away* from the presently claimed invention, and not as evidence of "unexpected results." There is no requirement under U.S. law that teaching-away evidence must be "commensurate in scope" with the claimed invention. In fact, since by definition a *teaching away* is a teaching in the art, it could not include all of the limitations of the claim or it would likely constitute an anticipatory reference and the obviousness question would be moot. As firmly established by the seminal Supreme Court case *United States v. Adams*, 383 U.S. 39 (1966), "Known disadvantages in old devices

which would naturally discourage the search for new inventions may be taken into account in determining obviousness." In the *Adams* case, the Court was referring to teachings in the art regarding disadvantages of various prior art batteries that shared some but not all features of the claimed battery. Those prior art batteries were certainly not "commensurate in scope" with Adams' claimed battery, yet the Court was quite willing to rely on the fact that the art describing those prior batteries taught away from the claimed battery as a basis for finding non-obviousness. Long after the holding in *Adams*, the Court of Appeals of the Federal Circuit described the standard for a *teaching away* as follows: "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006). Note also the holding in *Takeda Chemical Industries, LTD. v. Alphapharm PTY., LTD.*, 492 F.3d 1350, 1358-9 (Fed. Cir. 2007), which relied heavily on the teaching-away in a published article ("Sodha II") regarding the negative side effects of a prior art compound ("compound b") in finding that it would not have been obvious to select compound b and modify it to end up with the claimed compound, pioglitazone. Sodha II did not mention pioglitazone, so its teachings were certainly not "commensurate in scope" with the claims in that case. Sodha II was properly relied upon as a teaching-away because its teachings about the negative properties of prior art compound b "would have directed one of ordinary skill in the art away from that compound" as a starting compound, and thus away from making pioglitazone. *Id* at 1359.

In the present case, the prior art Pulmicort Turbuhaler® product insert taught one of ordinary skill that this budesonide-containing product should not be inhaled more than twice per day, never "as needed," and never altering the dose without a physician's specific instruction. These warnings, which stem at least in part from the recognized dangers of overdosing on corticosteroids, are consistent with Carling et al.'s teachings that the budesonide/formoterol combination should be inhaled just twice per day: "a twice daily dosing regime as a basic treatment of asthma" (Carling et al. at page 4, lines 20-21); "the intended dose regimen is a twice daily administration" (Carling et al. at page 6, lines 22-23). Since the prior art of record

consistently led one of ordinary skill "in a direction divergent from the path that was taken by the applicant," it meets the Federal Circuit's standard for a *teaching away* from the claimed methods, as set out in *Optivus Tech. v. Ion Beam Applications*. Accordingly, one of ordinary skill in the art would have had neither a motivation to carry out the presently claimed methods nor a reasonable expectation of success upon doing so. Applicant respectfully requests that the Examiner address the merits of Applicant's position that the teachings of the budesonide product insert constitute a *teaching-away* from the presently claimed methods, rather than dismissing this evidence for a reason that is not in accordance with U.S. law.

A second product insert that was cited in the July 27, 2007 Reply and has been discussed repeatedly in the Office actions and Replies since then is the Symbicort® Turbuhaler® budesonide/formoterol fumarate dihydrate product insert submitted as Exhibit 2 with the July 27, 2007 Reply. Exhibit 2 describes use of the Symbicort® product in a twice-per-day maintenance dosing regimen (similar to the dosing regimen for the Pulmicort® budesonide-only product that is the subject of the Exhibit 1 product insert discussed above). In prior Replies filed in this prosecution, Applicant has pointed to a number of passages from Exhibit 2 that support the nonobviousness of the presently claimed methods. Two of these are hand-labeled "D" and "E" on page 2 of Exhibit 2; together, these read as follows:

> **If patients find the treatment ineffective, or exceed the current dose of the fixed combination, medical attention must be sought. Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.**

According to the present Office action at page 15,

> In regards to Exhibit 2, the statements D and E verifies the Examiner's statement that patients will take more than the current dose if needed. Although the additional doses are not recommended, it is not impossible to not take an additional administration if the patient *feels the need* for treatment. In an asthma attack, if a patient is faced with not breathing and taking an additional administration within the safe inhalation amounts, one would find that the patient would take an as-needed administration. The statements in D and E show evidence that patients will take additional medication when needed without the doctor's advice. (Emphasis in the original)

It is unclear why the Examiner believes that the quoted passage of Exhibit 2 "verifies that patients will take more than the current dose if needed." By saying that if a patient exceeds the current dose of Symbicort, "medical attention must be sought," the quoted passage quite clearly communicates that exceeding the current dose is potentially dangerous and is not to be done under any circumstances. Perhaps the Examiner is reading the second sentence of the quoted passage (i.e., "**Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy**") as the "verification" of her position that "patients will take more than the current dose if needed" and as "[showing] evidence that patients will take additional medication when needed without the doctor's advice." Applicants point out that the "rescue bronchodilators" referred to in that sentence are not the Symbicort budesonide/formoterol combination, but rather a entirely separate category of inhaled bronchodilator drugs, the short-acting β2 agonists. Short-acting β2 agonists (e.g., terbutaline and albuterol) are utilized by asthma patients on an emergency basis, to quickly relieve the immediate symptoms of an asthma attack. Inhalers containing such short-acting β2 agonists are typically prescribed in addition to, and separate from, whatever maintenance treatment is prescribed. The patient is told to use the short-acting β2 agonist as needed, whenever he feels an attack is imminent, or if he is about to encounter symptom-inducing conditions (such as exercise or allergens). The quoted passage from Exhibit 2 is saying that increasing use of these short-acting β2 agonists (i.e., not Symbicort) indicates that the patient's asthma symptoms are worsening. Worsening symptoms in turn suggest that the patient's ongoing twice-daily maintenance treatment with Symbicort is not working as well as it should, so should be reassessed by the physician and perhaps adjusted by increasing the dosage or changing to a different medication. The quoted statements "D" and "E" do not even imply that the patient will ever use Symbicort (as opposed to a short-acting β2 agonist) on an as-needed basis. In fact, by saying that "medical attention must be sought" if the patient exceeds the prescribed dose of Symbicort, the quoted statements plainly imply the opposite.

Applicant reminds the Examiner that, prior to the present invention, inhaled glucocorticosteroids were never prescribed for use in an acute situation, since

glucocorticosteroids are not bronchodilators, were understood to be slow-acting and ineffective for relieving acute attacks, and present a significant risk of steroid overdosing if taken in a dosage that exceeds the fixed amount prescribed by the physician. See, for example, the statements in Exhibit 1 (the Pulmicort Turbuhaler product insert) labeled D and E:

> **PULMICORT TURBUHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measure are required.... PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma.**

See also the third column of the "Patient's Instructions for Use" on page 2 of Exhibit 1, which says, *inter alia*,

> **DO NOT inhale more doses or use your Turbuhaler more often than instructed by your doctor. This medicine is NOT intended to provide rapid relief of your breathing difficulties during an asthma attack. It must be taken at regular intervals as recommended by your doctor, and not as an emergency measure.** (Emphasis in the original)

Consistent with these teachings in Exhibit 1, Exhibit 2 makes it clear that the combination product in Symbicort Turbuhaler was to be administered as a regular maintenance treatment just twice per day, and if the patient suffered any acute asthma attacks despite this maintenance treatment, she was to use a <u>different</u> drug, a short-acting β2 agonist (not the Symbicort combination), as needed to relieve her symptoms. Thus, nothing in Exhibit 2 "verifies" the Examiner's assumption that patients would take additional doses of the Symbicort product "if needed." Asthma patients were told to inhale from their short-acting β2 agonist inhalers on an as-needed basis, to counteract an asthma attack. They were <u>not</u> told to inhale additional doses from their maintenance treatment inhalers on an as-needed basis, and in fact (as established above), taking more than the prescribed twice-daily maintenance dose of Symbicort was strictly forbidden: "**If patients ... exceed the current dose of the fixed combination, medical attention must be sought.**"

The Office action at pages 15-16 dismisses (yet again) the evidence in Exhibit 3 that was submitted with Applicant's July 27, 2007 Reply, on the ground that it concerns an admixture of two drugs different from those recited in the present claims. According to the Office action at

page 16, "In order to truly compare the two compositions both compounds need to be present. It is noted that evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention. See, e.g., In re Kulling…; In re Grasselli…." Thus, as was the case with respect to Exhibit 1, the Examiner appears to believe that Applicant intended Exhibit 3 to serve as evidence of "unexpected results." This is not why Applicant cited Exhibit 3. As stated in the July 27, 2007 Reply at pages 19-21, Exhibit 3 was offered as further evidence that glucocorticosteroid-containing products were not routinely utilized on an as-needed basis, even years after the present application's priority date. This evidence (along with that in Exhibits 1 and 2) contradicts the assumption underlying the obviousness rejection that one of ordinary skill in the art would have found it "obvious" to inhale Carling et al.'s glucocorticosteroid-containing product on an as-needed basis. Exhibit 3 is a "Patient's Instructions for Use" document relating to another combination product containing a glucocorticosteroid and a long-acting beta-2 agonist (Advair Diskus® fluticasone propionate/salmeterol xinafoate). As noted at page 20 of the July 27, 2007 Reply, Exhibit 3 emphasizes repeatedly that the product must be used neither more nor less often than instructed by the physician. The patient is adamantly instructed not to use the combination therapy more frequently than 2 times daily, spaced approximately 12 hours apart, and is told to inhale only the recommended dose of 1 inhalation each time. The patient is further instructed not to use the product to relieve sudden asthma symptoms. See Exhibit 3 and the more detailed discussion of it at pages 19-21 of the July 27, 2007 Reply. As should be apparent from that discussion, Applicant did not cite Exhibit 3 as evidence of "unexpected results," but rather as evidence that those of skill in the art understood that glucocorticosteroid-containing products should never be inhaled on an as-needed basis. The Examiner is asked to give this evidence proper consideration.

Pages 16-17 of the present Office action briefly address Exhibits 4 and 5 submitted with the July 27, 2007 Reply, stating that "the Examiner has considered the comments made by O'Byrne et al. and Barnes, but does not find that the evidence overcomes the prior art." According to the Office action, "Carling et al. teaches that the combination of budesonide and formoterol have greater efficiency and duration of bronchodilator action, and rapid onset action,

which provides rescue medicine, adequate dosing for treating asthma (see page 4, lines 4-21), thus the Applicant's results are not viewed as surprising."

Applicant points out that any teachings of Carling et al. regarding "advantages" of the budesonide/formoterol combination are advantages resulting from use of the combination in the treatment method explicitly taught by Carling et al. (*i.e., just twice daily*), in comparison with other asthma treatments that were then known in the art. Carling et al. did not contemplate supplementing the described twice-daily treatment with additional "as needed" use of the budesonide/formoterol combination, and certainly did not provide any reason to believe there might be <u>further</u> advantages, in addition to those disclosed for use of the combination twice daily, if one were to use the combination not only twice daily but take additional inhalations as needed. Applicant has provided several lines of evidence that use of the budesonide/formoterol combination as both a maintenance treatment and as a reliever medication inhaled as needed, as determined by the patient, provides dramatically surprising results when directly compared to use of the same combination in accordance with Carling et al.'s teachings, i.e., for twice-daily maintenance treatment alone (with a separate, short-acting β2 agonist bronchodilator inhaler employed as-needed). Thus, the surprising results obtained by Applicant are <u>in addition to</u> any advantages taught by Carling et al. for twice-per-day maintenance treatment alone. The significance and surprising nature of these results cannot be dismissed, as the Examiner has done, merely because Carling et al. said that twice-per-day treatment with the combination had advantages compared to other treatments then known in the art. Applicant asks that the Examiner reconsider the surprising results described in Exhibit 4 submitted with the July 27, 2007 Reply (i.e., the O'Byrne et al. article) and summarized in the July 27, 2007 Reply at pages 26-27. O'Byrne et al.[1] compared one group of patients taking the budesonide/formoterol combination for twice-per-day maintenance treatment and using a separate, short-acting β2 agonist (terbutaline) as-needed for relief of asthma symptoms, with a second group relying on the budesonide/formoterol combination <u>both</u> for twice-per-day maintenance treatment and as-needed for relief of symptoms (i.e., in accordance with the present claims). Nothing that

[1] The O'Byrne et al., study and the Kuna et al., Rabe et al., Bousquet et al., and Scicchitano et al. studies described below were supported by AstraZeneca, the assignee of the present application.

Carling et al. said about advantages with twice-per-day dosing with the budesonide/formoterol combination could have led one to expect the further, and quite dramatic, improvements seen in several measures of efficacy (such as the rate of exacerbations) in the second group of patients. The Examiner has not explained what in Carling et al. would have led one of ordinary skill in the art to expect these further improvements when the Carling et al. combination is utilized in a way that was not contemplated by Carling et al., particularly in view of the understanding in the prior art that budesonide and other glucocorticosteroids were not useful for immediate relief of symptoms and should not be administered on an as-needed basis.

New evidence

Applicants submit herewith as Appendices A-E several recently published studies, each providing further evidence of surprising results.

The first is Kuna et al., "Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations," Int J Clin Pract 61:725-736 (2007) (Appendix A). As in O'Byrne et al., the Kuna et al. study showed a dramatic reduction in asthma exacerbations achieved with treatment in accordance with the claimed methods, compared to treatment in accordance with Carling et al.'s twice-per-day maintenance regimen. The new study investigated whether this reduction in exacerbations might be attributable to the fact that patients treated in accordance with the claimed methods ultimately received a higher total daily dose of budesonide/formoterol than those on a maintenance-only regimen. In the Kuna et al. study, one group of patients inhaled a maintenance dose of 160 μg budesonide and 4.5 μg formoterol fumarate dihydrate from an inhaler twice per day, every day, plus additional inhalations of the same combination as needed for relief of asthma attacks, as determined by the patient. That treatment was referred to as "SMART" (short for "Symbicort® Maintenance And Reliever Therapy"). A second group of patients inhaled a maintenance dose of 320 μg budesonide and 9 μg formoterol fumarate dihydrate twice per day (i.e., double the maintenance dose given to the "SMART" group) and used terbutaline (not budesonide/formoterol) as an as-needed reliever

medication. The patients in that second group, referred to by Kuna et al. as the "budesonide/formoterol" group, received a total of **640 μg budesonide and 18 μg formoterol fumarate dihydrate** per day over the course of the study, compared to the average total of only **483 μg budesonide and 13.6 μg formoterol fumarate dihydrate** per day administered to the patients of the "SMART" group. See Figure 5 on page 733. Despite receiving an overall lower total daily dose of budesonide/formoterol (and no terbutaline at all) compared to the second group, the "SMART" group suffered far fewer severe exacerbations than did the second group. See Table 2 on page 730, which reports that the SMART group had a total of **125** severe exacerbations (adding up to a total of 692 days of exacerbations) during the study, while the "budesonide/formoterol" group had **173** severe exacerbations, adding up to a total of 1143 days of exacerbations. Thus, even though the "SMART" group received only 75% of the total daily dose of budesonide/formoterol received by the second group, and were given no terbutaline at all, the rate of severe exacerbations in the "SMART" group was 28% lower than the rate in the second group. ***Nothing in Carling et al., nor in any other prior art, could have predicted such a counterintuitive result.***

Further surprising results can be found in Rabe et al., Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study," Lancet 368:744-753 (2006) (Appendix B). Rabe et al. divided his patients into three groups, all three of which received the same twice-daily maintenance treatment with a budesonide/formoterol combination inhaler, but different reliever therapies for as-needed use: one group used budesonide/formoterol as the reliever (as well as for maintenance treatment), the second used formoterol as the reliever, and the third used terbutaline as the reliever. Consistent with O'Byrne et al.'s results, Rabe et al. found a much lower rate of exacerbations in patients who used the budesonide/formoterol combination both for maintenance and for as-need relief, compared to patients in the third group who used the combination solely for maintenance and used terbutaline for as-needed relief. See Table 2 on page 748 of Rabe et al. The same Table 2 also shows that using the budesonide/formoterol combination as a reliever was

superior to using formoterol alone as the reliever, illustrating that the benefit of the combination when used as a reliever is not entirely attributable to the formoterol component of the combination. (Since formoterol is a bronchodilator and budesonide is not, it would have been reasonable to expect the improvement seen with the combination to be entirely attributable to formoterol.) See also the graph in Figure 2. ***Given the teachings in the art that budesonide and other glucocorticosteroids are of no use as reliever medications because of their lack of bronchodilatory effect and the long time it takes for them to exert their anti-inflammatory effects, it was surprising to find that the budesonide/formoterol combination was superior to formoterol alone as a reliever medication, when each was used in conjunction with budesonide/formoterol maintenance therapy.***

More surprising results are reported in the papers enclosed as Appendices C and D. Appendix C is Scicchitano et al., "Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma," Curr Med Res Opin 20(9):1403-1418 (2004). Appendix D is Bousquet et al., "Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone," Resp Med 101:2437-2446 (2007). Each of these studies compared methods in accordance with the present invention to other methods of treating asthma, and found that the presently claimed methods were far superior in reducing the number of exacerbations, as well as by other measures of efficacy, ***even though the patients treated in accordance with the presently claimed methods received a much lower total dose of inhaled corticosteroid.***

Finally, as further objective evidence of nonobviousness, Applicant brings to the Examiner's attention a recent opinion piece attesting to the impact the presently claimed invention has had on asthma therapy: D'Urzo, "Inhaled Glucocorticosteroid and Long-Acting β2-Adrenoceptor Agonist Single-Inhaler Combination for Both Maintenance and Rescue Therapy," Treat Respir Med 5:385-391 (2006) (Appendix E). According to D'Urzo,

> **The use of a single inhaler (budesonide/formoterol) for both maintenance and reliever therapy represent a significant paradigm shift in asthma management that is simple and effective.** (page 389, last paragraph)

D'Urzo refers to this as "**a novel strategy**" (page 390, first full paragraph), and opines:

> **The concept of single-inhaler maintenance and reliever therapy represents one of the most important advances in asthma management in many years, and one that appears particularly well suited for utilization in the primary care setting**. (page 390, last paragraph)

Thus, D'Urzo adds his voice to that of Peter J. Barnes, M.D., who wrote in the editorial submitted as Exhibit 5 with the July 27, 2007 Reply that the O'Byrne et al. results were "**remarkable**" and "**surprisingly good results**" that "**may lead to changes in the paradigm of asthma management**." See the discussion of the Barnes editorial on pages 27-28 of the July 27, 2007 Reply. Plainly neither D'Urzo nor Barnes (both experts in the field) viewed use of budesonide/formoterol combination in accordance with the present claims to have been "obvious" in view of standard asthma therapy, i.e., therapy in which a glucocorticosteroid (whether alone or in combination with a second agent) is used solely for maintenance treatment, never as-needed as a reliever.

Summary

Applicant has addressed above several points raised in the present Office action and has presented new objective evidence of nonobviousness for the Examiner's consideration. It is believed that the arguments and evidence discussed above, together with arguments and evidence already of record (all of which is incorporated by reference here), incontrovertibly establish the nonobviousness of the present claims over Carling et al. alone or Carling et al. taken with Aberg et al. and Ryrfeldt et al. Withdrawal of the rejections and allowance of the claims are respectfully requested.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing attorney docket no. 06275-0188002.

Respectfully submitted,

Date: June 3, 2010

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Customer Number 26164
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22403621.doc